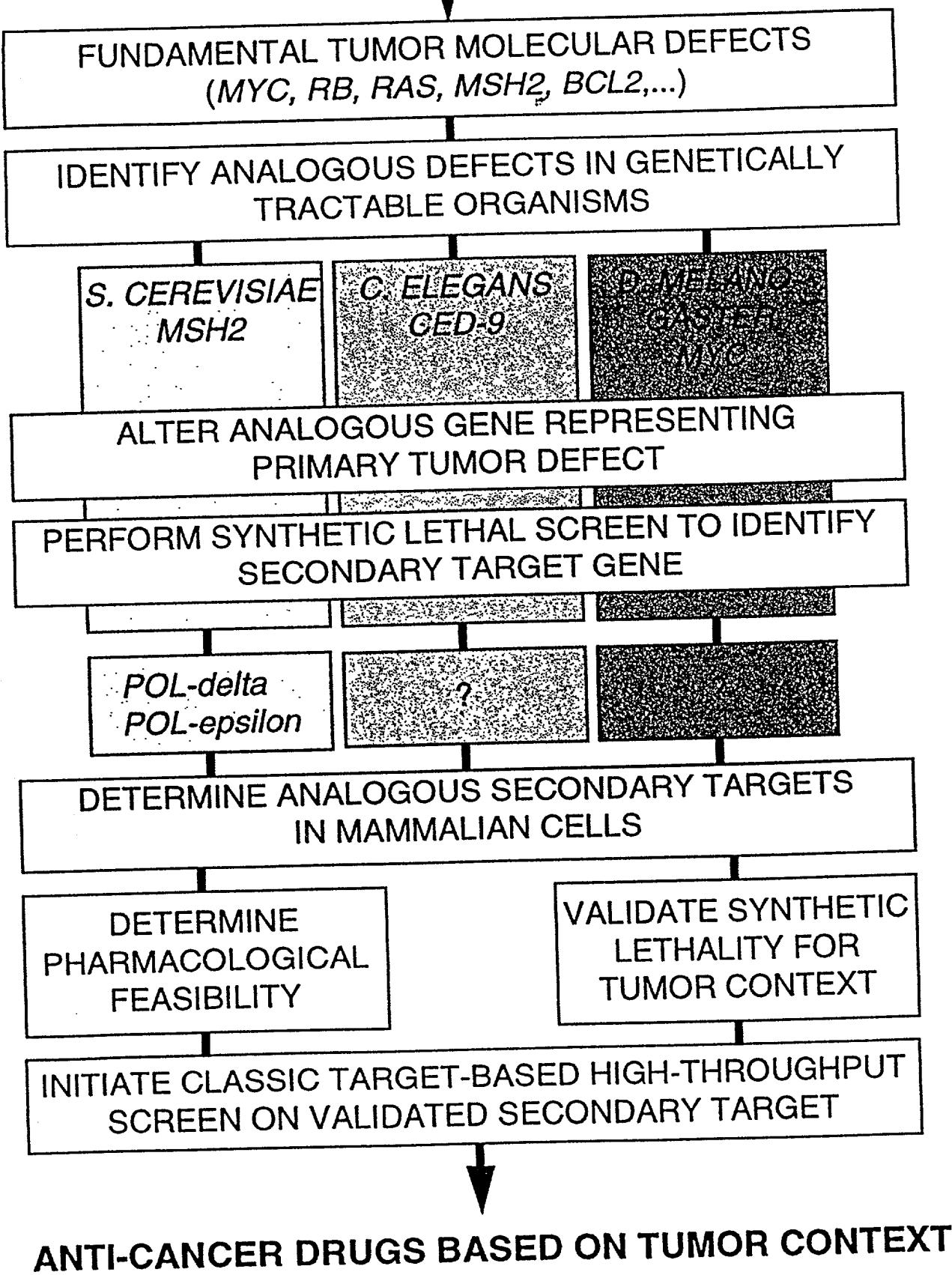
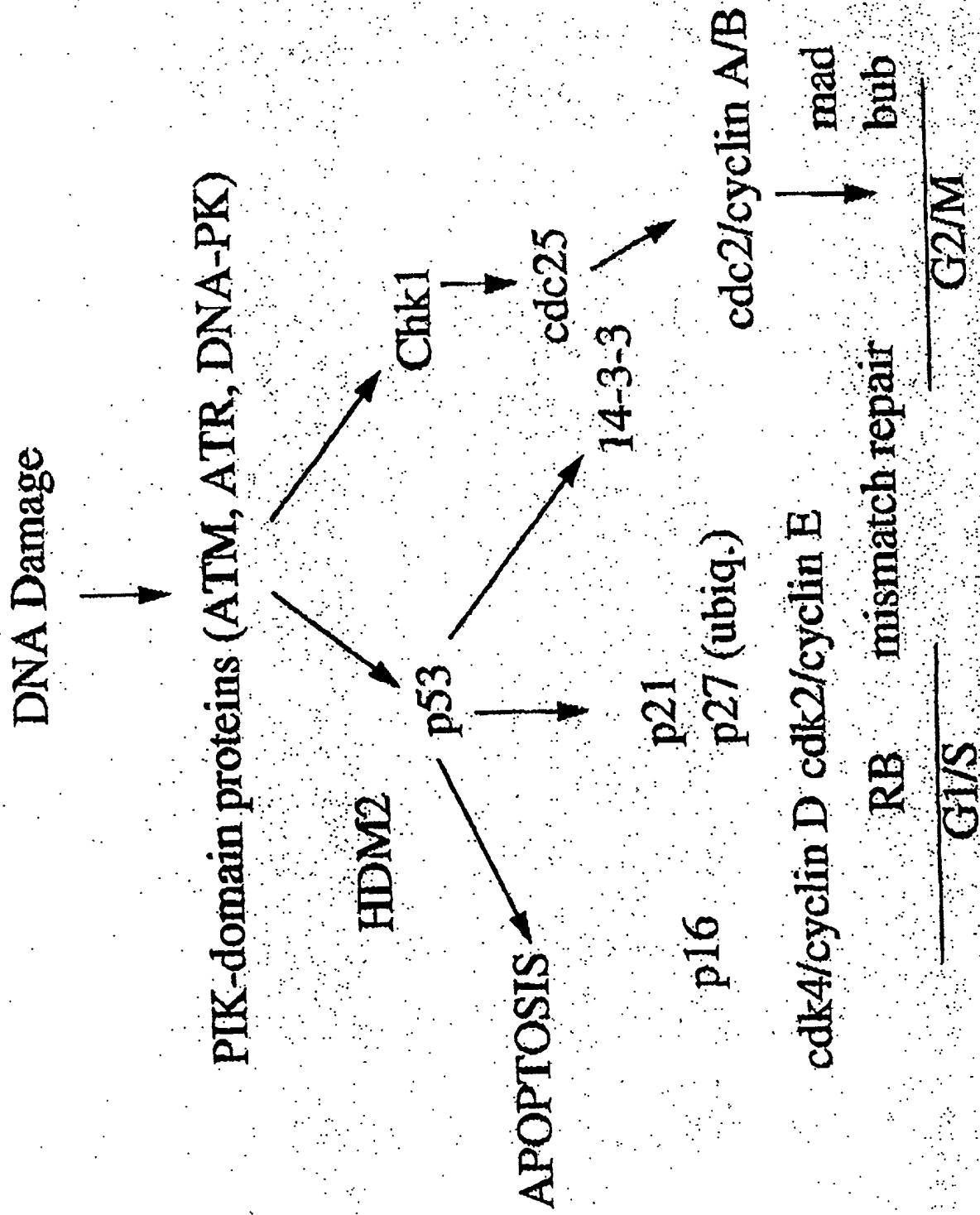


# MOLECULAR ALTERATIONS IN TUMORS



# Cell Cycle/DNA Damage Response Pathways

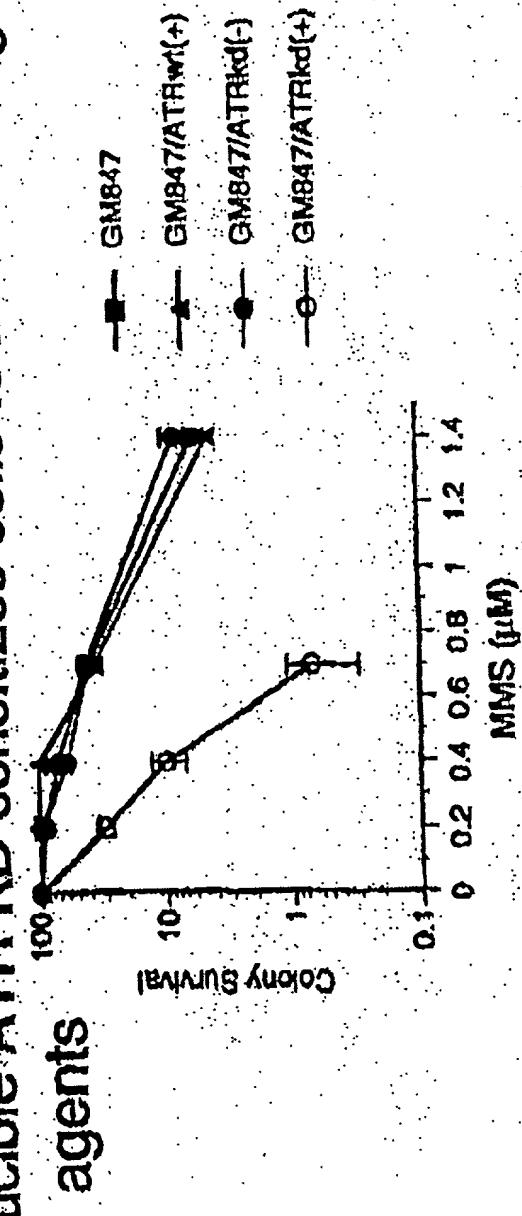
Figure 2



# MAMMALIAN CELL EVALUATION OF ATR AS A TARGET

1. Overexpression of ATR-KD not tolerated in human tumor cell lines (MCF-7, A549)

2. Inducible ATR-KD sensitizes cells to DNA damaging agents



3. LCK promoter driven ATR-KD transgenic mice have cells stably expressing ATR-KD in thymus

Figure 4

## Synthetic lethality:

- Use primary defect as a selective context to kill tumor cells with an alteration in gene A.
- Combined defects in gene A and gene B kill tumor cells while disrupting gene B activity alone has no effect on normal cells.

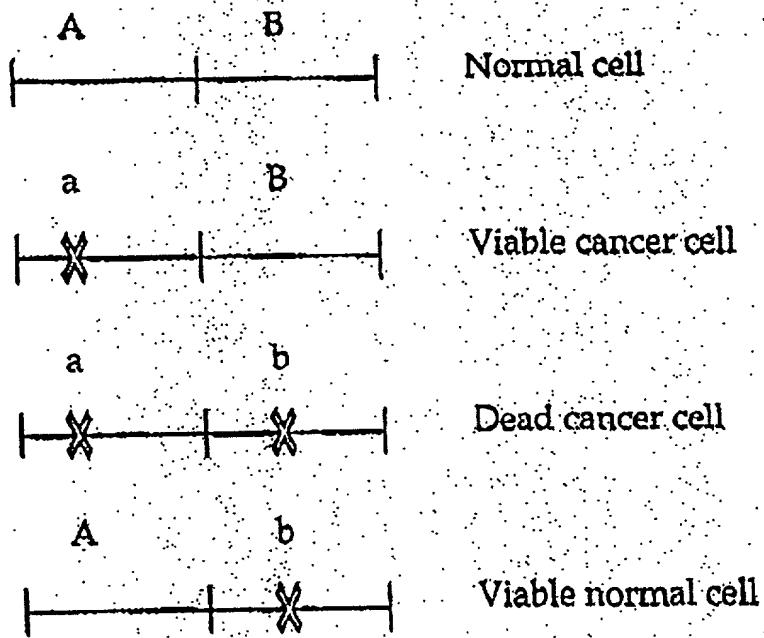


Figure 5

Human genes altered in tumors and their relatives in model genetic systems. Genes that are not structural homologs but act in analogous pathways (such as human p53 and *S. cerevisiae RAD9*) are shown in brackets. *Saccharomyces cerevisiae* genes are designated with superscript Sc, *S. pombe* with Sp, *C. elegans* with Ce, and *D. melanogaster* with Dm. Because of space limitations, this is only a representative list of genes mutated in tumors that have genetic analogs in model systems.

| Function                               | Human genes         | Model system analogs:<br>structural homologs or<br>related biological roles                  |
|--|---------------------|--|
| DNA damage checkpoint                  | p53                 | [RAD9 <sup>Sc</sup> , rad1 <sup>+</sup> Sp]  |
|  | ATM                 | MEC1 <sup>Sc</sup> , TEL1 <sup>Sc</sup> ,<br>rad3 <sup>3+Sp</sup> , mei-41 <sup>Dm</sup>     |
| DNA mismatch repair                    | MSH2, MLH1          | MSH2 <sup>Sc</sup> , MLH1 <sup>Sc</sup>  |
| Nucleotide excision repair             | XP-A, XP-B          | RAD14 <sup>Sc</sup> , RAD25 <sup>Sc</sup>  |
| O <sup>6</sup> -methylguanine reversal | MGMT                | MGT1 <sup>Sc</sup>   |
| Double-strand break repair             | BRCA2, BRCA1        | [RAD51 <sup>Sc</sup> , RAD54 <sup>Sc</sup> ]   |
| DNA helicase                           | BLM                 | SGS1 <sup>Sc</sup> , rgh1 <sup>+</sup> Sp  |
| Growth factor signaling                | RAS                 | RAS1 <sup>Sc</sup> , RAS2 <sup>Sc</sup> ,<br>let-60 <sup>Co</sup>                            |
|  | NF1                 | IRA1 <sup>Sc</sup> , IRA2 <sup>Sc</sup>  |
|  | MYC                 | dMyc <sup>Dm</sup>   |
|  | PTH                 | patched <sup>Dm</sup>  |
| Cell cycle control                     | Cyclin D, Cyclin E  | CLN1 <sup>Sc</sup> , CLN2 <sup>Sc</sup> ,<br>Cyclin D <sup>Dm</sup> , Cyclin E <sup>Dm</sup> |
|  | P27 <sup>Kip1</sup> | [SIC1 <sup>Sc</sup> ]  |
|  | Rb                  | Rbf <sup>Dm</sup>  |
| Apoptosis                              | BCL-2               | ced-9 <sup>Co</sup>  |

# Cell Cycle/DNA Damage Response Pathways

DNA Damage

PIK-domain proteins (ATM, ATR, DNA-PK)

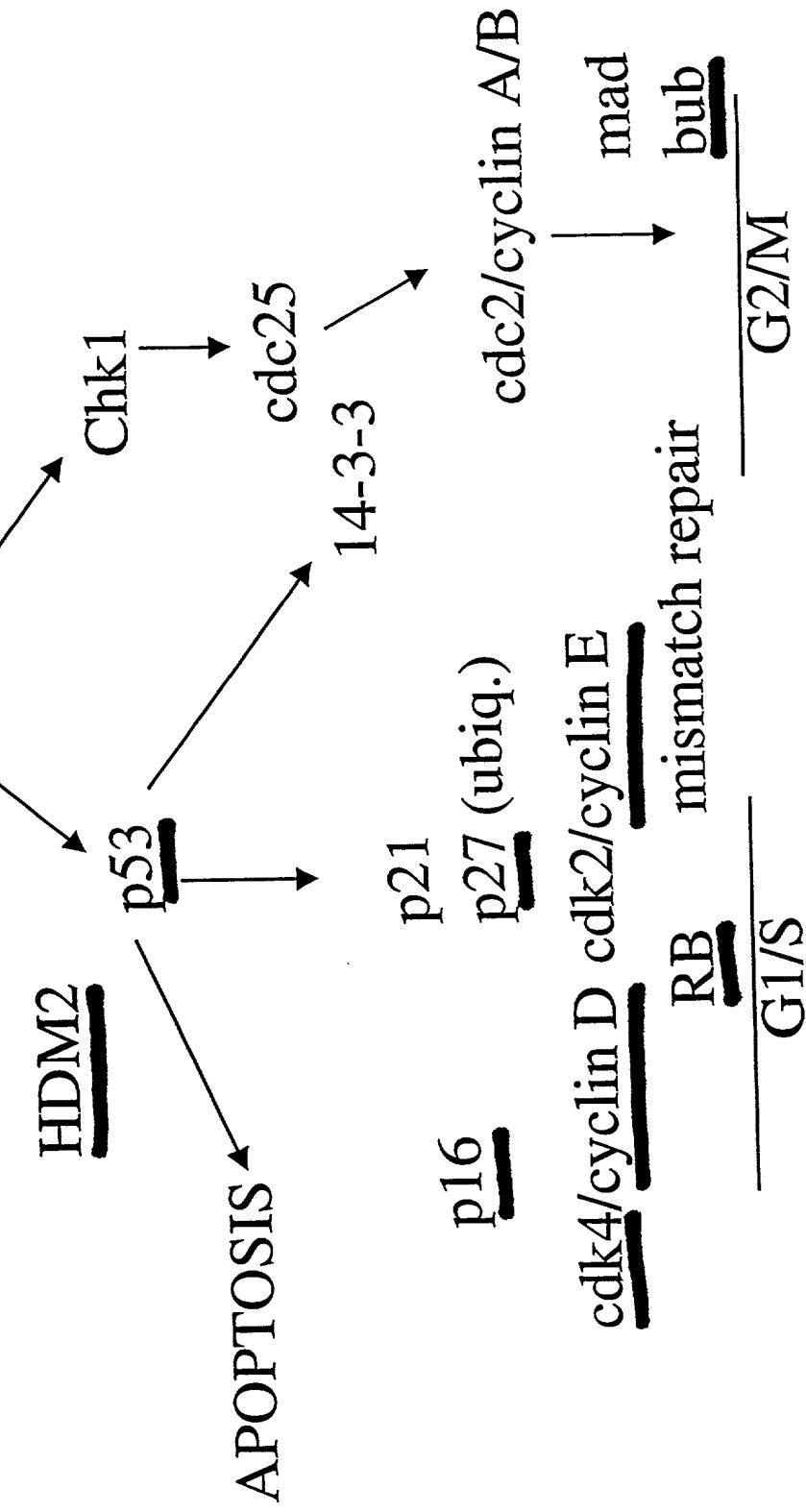


Figure 7

